

CLAIMS

1. A method for genetically altering a subject comprising the steps of genetically modifying cells, wherein the cells are selected from HSC, lymphoid progenitor cells, myeloid progenitor cells, epithelial stem cells and combinations thereof, and delivering them to the 5 patient, while the patient's thymus is undergoing reactivation.

2. The method of claim 1 further comprising the step of T cell ablation prior to administration of cells.

3. The method of claim 1 wherein the patient's thymus has been at least in part deactivated.

10 4. The method of claim 3 wherein the patient is post-pubertal.

5. The method of claim 3 wherein the patient has or had a disease or treatment of a disease that at least in part deactivated the patient's thymus.

6. The method of claim 1 wherein the cells are from the patient.

7. The method of claim 1 wherein the cells are not from the patient.

15 8. The method of claim 1 wherein the patient has a T cell disorder.

9. The method of claim 8 wherein the T cell disorder is caused by a condition selected from the group consisting of T cell functional disorder, HIV infection, and T cell leukemia virus infection.

10. The method of claim 9 wherein the cells are genetically modified to inhibit 20 infection of the cells by virus.

11. The method of claim 9 wherein the cells are genetically modified to inhibit replication of virus within T cells.

12. The method of claim 9 wherein the T cell disorder is caused by HIV infection.

13. The method of claim 12 wherein the cells are genetically modified to include a stably expressible polynucleotide selected from the group consisting of a nef transcription factor gene, a gene that codes for a ribozyme that cuts HIV *tat* and/or *rev* genes, the trans-dominant mutant form of HIV-1 *rev* gene (RevM10), an overexpression construct of the HIV-1 *rev*-responsive element (RRE), and function fragments thereof.

5 14. The method of claim 1 wherein the HSC are CD34⁺.

15. The method of claim 1 wherein the genetically modified cells are provided to the patient about the time when the thymus begins to reactivate or shortly thereafter.

16. The method of claim 1 wherein the method of disrupting the sex steroid mediated 10 signaling to the thymus is through administration of one or more pharmaceuticals.

17. The method of claim 11 wherein the pharmaceuticals are selected from the group consisting of LHRH agonists, LHRH antagonists, anti-LHRH vaccines and combinations thereof.

18. The method of claim 12 wherein the LHRH agonists are selected from the group 15 consisting of Eulexin, Goserelin, Leuprolide, Dioxalan derivatives, Triptorelin, Meterelin, Buserelin, Histrelin, Nafarelin, Lutrelin, Leuprorelin and Deslorelin.

19. A method for preventing infection of a patient by HIV comprising the steps of T cell ablation, disruption of sex steroid mediated signaling to the thymus, and administration of 20 genetically modified cells, wherein the genetically modified cells are selected from genetically modified HSC, lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

20. The method of claim 19 wherein the genetically modified cells contain a stably expressible polynucleotide that prevents infection of a T cell by HIV.

21. The method of claim 20 wherein the stably expressible polynucleotide is selected from the group consisting of a nef transcription factor gene, a gene that codes for a ribozyme that 25 cuts HIV *tat* and/or *rev* genes, the trans-dominant mutant form of HIV-1 *rev* gene (RevM10),

and an overexpression construct of the HIV-1 *rev*-responsive element (RRE), and functional fragments thereof.

22. The method of claim 19 wherein the HSC are CD34⁺.

23. The method of claim 19 wherein the genetically modified cells are provided to the
5 patient about the time when the thymus begins to reactivate or shortly thereafter.

24. The method of claim 19 wherein the method of disrupting the sex steroid
mediated signaling to the thymus is through administration of one or more pharmaceuticals.

25. The method of claim 24 wherein the pharmaceuticals are selected from the group
consisting of LHRH agonists, LHRH antagonists, anti-LHRH vaccines and combinations
10 thereof.

26. The method of claim 25 wherein the LHRH agonists are selected from the group
consisting of Eulexin, Goserelin, Leuprolide, Dioxalan derivatives, Triptorelin, Meterelin,
Buserelin, Histrelin, Nafarelin, Lutrelin, Leuprorelin and Deslorelin.

27. A method for genetically altering a patient comprising:

15 reactivating the thymus of the patient;

genetically modifying cells *in vitro*; and

administering the genetically modified cells to the patient;

wherein the cells are selected from the group consisting of stem cells, progenitor cells,
and combinations thereof.

20 28. The method of claim 27, wherein the thymus of the patient has been at least in
part atrophied before it is reactivated.

29. The method of claim 28, wherein the patient has a disease that at least in part
atrophied the thymus of the patient.

30. The method of claim 28, wherein the patient has had a treatment of a disease that at least in part atrophied the thymus of the patient.

31. The method of claim 30, wherein the treatment is immunosuppression, chemotherapy or radiation treatment.

5 32. The method of claim 28, wherein the patient is post-pubertal.

33. The method of claim 27, wherein the stem cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

34. The method of claim 27, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

10 35. The method of claim 33, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

36. The method of claim 33, wherein the cells are hematopoietic stem cells.

37. The method of claim 36, wherein the hematopoietic stem cells are CD34+.

38. The method of claim 36, wherein the hematopoietic stem cells are autologous.

15 39. The method of claim 36, wherein the hematopoietic stem cells are not autologous.

40. The method of claim 37, wherein the genetically modified hematopoietic stem cells are administered when the thymus begins to reactivate.

41. The method of claim 27, wherein the thymus is reactivated by disruption of sex steroid-mediated signaling to the thymus.

20 42. The method of claim 41, wherein the stem cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

43. The method of claim 41, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

44. The method of claim 42, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

45. The method of claim 42, wherein the cells are hematopoietic stem cells.

46. The method of claim 45, wherein the genetically modified hematopoietic stem
5 cells are administered at the time disruption of sex steroid-mediated signaling to the thymus is begun.

47. The method of claim 41, wherein the sex steroid-mediated signaling to the thymus is disrupted by surgical castration.

48. The method of claim 41, wherein the sex steroid-mediated signaling to the thymus
10 is disrupted by chemical castration.

49. The method of claim 41, wherein the sex steroid-mediated signaling to the thymus is disrupted by administration of one or more pharmaceuticals.

50. The method of claim 49, wherein the one or more pharmaceuticals is selected
from the group consisting of LHRH agonists, LHRH antagonists, anti-LHRH vaccines, anti-
15 androgens, anti-estrogens, SERMs, SARMs, SPRMs, ERDs, aromatase inhibitors, anti-
progesterogens, and combinations thereof.

51. The method of claim 50, wherein the LHRH agonists are selected from the group
selected from the group consisting of Eulexin, Goserelin, Leuprolide, Dioxalan derivatives,
Triptorelin, Meterelin, Buserelin, Histrelin, Nafarelin, Lutrelin, Leuprorelin, Deslorelin,
20 Cystorelin, Decapeptyl, Gonadorelin, and combinations thereof.

52. The method of claim 50, wherein the LHRH antagonists are selected from the
group consisting of Abarelix, Cetrorelix, and combinations thereof.

53. The method of claim 27, wherein the patient is infected with a virus.

54. The method of claim 53, wherein the virus is selected from the group consisting
25 of Retroviridae, Picornaviridae, Calciviridae, Togaviridae, Flaviridae, Coronaviridae,

Rhabdoviridae, Filoviridae, Paramyxoviridae, Orthomyxoviridae, Bungaviridae, Arenaviridae, Reoviridae, Birnaviridae, Hepadnaviridae, Parvoviridae, Papovaviridae, Adenoviridae, Herpesviridae, Poxviridae, and Iridoviridae.

55. The method of claim 27, wherein the patient is infected with a human
5 immunodeficiency virus.

56. The method of claim 55, wherein the cells are genetically modified to inhibit
infection of the cells by the virus or to inhibit replication of the virus in the cells.

57. The method of claim 56, wherein the cells are CD34+ hematopoietic stem cells.

58. The method of claim 56, wherein the cells are genetically modified with a gene
10 selected from the group consisting of RevM10, CXCR4, and PolyTAR.

59. The method of claim 58, wherein the gene is RevM10.

60. The method of claim 27, further comprising ablating the T cells of the patient
prior to reactivating the thymus and administering the genetically modified cells to the patient.

61. The method of claim 27, further comprising administering at least one cytokine, at
15 least one growth factor, or a combination of at least one cytokine and at least one growth factor
to the patient.

62. The method of claim 61, wherein the cytokine is selected from the group
consisting of Interleukin 2 (IL-2), Interleukin 7 (IL-7), Interleukin 15 (IL-15), and combinations
thereof.

20 63. The method of claim 61, wherein the growth factor is selected from the group
consisting of members of the epithelial growth factor family, members of the fibroblast growth
factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte
growth factor (KGF), and combinations thereof.

25 64. The method of claim 62, wherein the growth factor is selected from the group
consisting of members of the epithelial growth factor family, members of the fibroblast growth

factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), and combinations thereof.

65. A method of preventing human immunodeficiency virus infection in a patient, comprising:

5 ablating the T cells of the patient;

reactivating the thymus of the patient;

genetically modifying cells *in vitro* with a gene that inhibits infection, replication or function of human immunodeficiency virus; and

administering the genetically modified cells to the patient,

10 wherein the cells are selected from the group consisting of stem cells, progenitor cells, and combinations thereof.

66. The method of claim 65, wherein the stem cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

67. The method of claim 65, wherein the progenitor cells are selected from the group 15 consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

68. The method of claim 66, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

69. The method of claim 65, wherein the thymus is reactivated by disruption of sex steroid-mediated signaling to the thymus.

20 70. The method of claim 65, further comprising treating the patient with anti-retroviral therapy.

71. The method of claim 70, wherein the anti-retroviral therapy is Highly Active Retroviral Therapy (HAART).

72. A method of treating human immunodeficiency virus infection in a patient, comprising:

ablatiing the T cells of the patient;

reactivating the thymus of the patient;

5 genetically modifying cells *in vitro* with a gene that inhibits infection, replication or function of human immunodeficiency virus; and

administering the genetically modified cells to the patient,

wherein the cells are selected from the group consisting of stem cells, progenitor cells, and combinations thereof.

10 73. The method of claim 72, wherein the stem cells are selected from the group consisting of hematopoietic stem cells, epithelial stem cells, and combinations thereof.

74. The method of claim 72, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

15 75. The method of claim 73, wherein the progenitor cells are selected from the group consisting of lymphoid progenitor cells, myeloid progenitor cells, and combinations thereof.

76. The method of claim 72, wherein the thymus is reactivated by disruption of sex steroid-mediated signaling to the thymus.

77. The method of claim 72, further comprising treating the patient with anti-retroviral therapy.

20 78. The method of claim 77, wherein the anti-retroviral therapy is Highly Active Retroviral Therapy (HAART).

79. A method for delivering a sex steroid analog to a patient, comprising:

laser-irradiating the skin of the patient to create perforations or alterations in the skin,
and

placing the sex steroid analog on the irradiated skin,

wherein the sex steroid analog is delivered through the perforations or alterations in the
5 irradiated skin.

80. A method for delivering a sex steroid analog to a patient, comprising:

delivering the sex steroid analog to the skin of the patient, and

permeabilizing the skin of the patient with high pressure impulse transients,

wherein the impulse transients cause the sex steroid analog to diffuse through the
10 permeabilized skin of the patient.

81. A method for enhancing transplantation of donor hematopoietic stem cells into
the thymus of a recipient patient, comprising:

depleting the T cells of the patient,

reactivating the thymus of the patient, and

15 transplanting donor hematopoietic stem cells to the patient,

wherein uptake of the donor hematopoietic stem cells into the patient's thymus is
enhanced as compared to the uptake that would have otherwise occurred in a patient prior to
thymus reactivation.

82. A method for increasing virus-specific peripheral T cell responsiveness of a
20 patient with an at least partially atrophied thymus, comprising:

reactivating the thymus of the patient,

exposing the patient to a virus,

determining the virus-specific peripheral T cell responsiveness in the patient,
wherein the patient has an increased viral-specific peripheral T cell responsiveness as
compared to the responsiveness that would have otherwise occurred in a patient prior to thymus
reactivation.

5